The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 37

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GARY L. CLAYMAN

Appeal No. 2000-0742
Application 08/758,033[1]

HEARD November 8, 2001

Before WINTERS, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

REMAND TO THE EXAMINER

This appeal concerns claims 1-14, 16-20, 26-32, 36, and 37, which the examiner has rejected under 35 U.S.C. § 103 as being obvious over certain prior art references. We conclude that the examiner's rejection does not rely on the most relevant prior art in the record. Therefore, we vacate the rejection on appeal and remand the application to the examiner.

[1] Application for patent filed November 27, 1996. The instant application claims the benefit of priority under 35 U.S.C. § 119(e)(1) based on provisional application 60/007,810, filed November 30, 1995.

Claim 1 is representative of the subject matter on appeal and reads as follows:

1. A method of inhibiting growth of a p53-positive tumor cell in a mammalian subject with a solid tumor comprising the steps of:

(a) providing a viral expression construct comprising a promoter functional in eukaryotic cells and a polynucleotide encoding a functional p53 polypeptide, wherein said polynucleotide is positioned sense to and under the control of said promoter; and

(b) directly administering said viral expression construct to said tumor in vivo, the administration resulting in expression of said functional p53 polypeptide in cells of said tumor and inhibition of tumor cell growth,

wherein said tumor comprises cells that express a functional p53 polypeptide.

The examiner relies on the following references:

Bramwell, "The role of chemotherapy in multimodality therapy," Canadian Journal of Surgery, Vol. 31, No. 5, pp. 390-396 (1988)

Cajot et al. (Cajot), "Growth suppression mediated by transfection of p53 in Hut292DM human lung cancer cells expressing endogenous wild-type p53 protein," Cancer Research, Vol. 52, No. 24, pp. 6956-6960 (1992)

Liu et al. (Liu), "Growth suppression of human head and neck cancer cells by the introduction of a wild-type p53 gene via a recombinant adenovirus," Cancer Research, Vol. 54, pp. 3662-3667 (1994)

Wills et al. (Wills), "Development and characterization of recombinant adenoviruses encoding human p53 for gene therapy of cancer," Human Gene Therapy, Vol. 5, pp. 1079-1088 (1994)

Zhang et al. (Zhang), "Gene therapy strategies for cancer," Exp. Opin. Invest. Drugs, Vol. 4, No. 6, pp. 487-514 (1995)

In the Final Rejection, the examiner also relied on the following references, which were withdrawn in response to a 131 declaration (Paper No. 25, filed November 9, 1999):

Katayose et al. (Katayose), "Cytotoxic effects of adenovirus-mediated wild-type p53 protein expression in normal and tumor mammary epithelial cells," Clinical Cancer Research, Vol. 1, pp. 889-897 (August 1995).

Srivastava et al. (Srivastava), "Recombinant adenovirus vector expressing wild-type p53 is a potent inhibitor of prostate cancer cell proliferation," Urology, Vol. 46, No. 6, pp. 843-848 (1995).

Claims 1-14, 16-20, 26-32, 36, and 37 stand rejected under 35 U.S.C. § 103 as obvious over the combined disclosures of Cajot, either of Wills or Liu, and either of Zhang or Bramwell.

We vacate and remand.

Background

1. Technical Background

Appellant's specification discloses a method of treating squamous cell carcinoma by administering an expression construct encoding the tumor suppressor p53. See page 3. The specification states that the "endogenous p53 of the squamous cell carcinoma may or may not be mutated." Id. The claims on appeal are directed to a disclosed embodiment that comprises treating cancer cells in which the endogenous p53 is not mutated, i.e., treating $p53^{+}$ tumor cells by administration of a construct which expresses p53.

Regarding this embodiment, the specification states that

> it has now been observed that p53 gene therapy of cancers may be effective regardless of the p53 status of the tumor cell. Surpisingly, therapeutic effects have been observed when a viral vector carrying the wild-type p53 gene is used to treat a tumor, the cells of which express a functional p53 molecule. This result would not have been predicted based on the current understanding of how tumor suppressors function. It also is surprising given that normal cells, which also express a functional p53 molecule, are apparently unaffected by expression of high levels of p53 from a viral construct.

Id., page 7.

2. Procedural Background

In the examiner's Final Office Action, all of the claims on appeal were rejected under 35 U.S.C. § 103 as obvious over the combination of Cajot, either of Katayose or Srivastava, either of Wills or Liu, and either of Zhang or Bramwell. See Paper No. 17, mailed April 12, 1999, page 7.

In response, Appellant filed a declaration under 37 CFR § 1.131. See Paper No. 25, filed November 9, 1999. In his declaration, Appellant stated that he had published research papers in January 1995 and July 1995 that "reported the Ad-p53 infection of cell lines with both mutated and wild-type p53."[2] Paragraph 3. He also stated that he understood "that the Examiner in charge of examining the referenced application has

[2] The papers relied on are Liu et al., "Apoptosis induction mediated by wild-type p53 adenoviral gene transfer in squamous cell carcinoma of the head and neck," Cancer Research, Vol. 55, pp. 3117-3122 (July 15, 1995) and Clayman et al., "In vivo molecular therapy with p53 adenovirus for microscopic residual head and neck squamous cell carcinoma," Cancer Research, Vol. 55, pp. 1-6 (January 1, 1995).

previously taken the position that these papers teach the use of adeno-p53 in the therapy of tumors in vivo, including the therapy of p53-positive tumor cells." Id.[3]

Appellant also stated in his declaration that the 1995 research papers "demonstrate that [he] had achieved the subject matter they disclose in the United States at least as of their date of publication, the earliest publication date as between the two being January, 1995." Paragraph 4. He also noted that Katayose and Srivastava were published after January 1995 and concluded that "[b]ased on the earlier publication of [the] two articles referenced above, it is clear that [he] had in [his] possession at least equivalent, and indeed more extensive, data than is taught in the Katayose and Srivastava references at a time prior to their respective publication dates." Paragraph 5.

In response to the 131 declaration, the examiner withdrew her reliance on Katayose and Srivastava. See the Examiner's Answer, page 20.

Discussion

1. The rejection on appeal.

The claims stand rejected as obvious over the combined disclosures of Cajot, either of Wills or Liu, and either of Zhang or Bramwell. Cajot teaches transfection of human lung cancer cells with a plasmid vector expressing p53. The tumor cells

[3] Appellant cites an "Office Action of 2/17/99" as supporting his position. The file record, however, shows no Office Action that was mailed February 17, 1999, although one was mailed February 17, 1998. We

(Hut292DM) used by Cajot express endogenous p53. Cajot found that "growth suppression [was] induced by high level expression of exogenous wild-type p53 in lung cancer cells expressing normal endogenous p53 protein." Page 6956, right hand column. Cajot concluded that his "work extends the scope of the potential effectiveness of wild-type p53 to control tumor growth to recipient cells that contain no apparent defect in endogenous wild-type p53 expression." Page 6959, right-hand column.

As the examiner notes, however, Cajot does not teach "in vivo transduction with a viral expression construct encoding p53." Examiner's Answer, page 11. The examiner relies on the secondary references to remedy this deficiency. Liu and Wills both teach inhibiting the growth of $p53^-$ tumor cells in vivo by administering recombinant adenovirus constructs encoding p53. See Liu, page 3662, abstract ("In vivo studies in nude mice with established s.c. squamous carcinoma nodules showed that tumor volumes were significantly reduced in mice that received peritumoral infiltration of Ad5CMV-p53."); Wills, page 1079, abstract ("Continued treatment of H69 tumors with MLP/p53 recombinant led to reduced tumor growth and increased survival time.").[4]

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understand this 1998 Office action to be the one referred to by Appellant.

[4] Zhang and Bramwell are relied on for teaching the treatment of cancer by a combination of two or more therapeutic approaches (gene therapy, radiation, chemotherapy, etc.). These references are relevant to some of the dependent claims on appeal but are not required for the prima facie case with respect to representative claim 1.

The examiner concluded that it would have been obvious, in view of the combined teachings of these references, to "treat a tumor which comprises cells that express a functional p53 polypeptide with adenoviral vectors encoding p53 polypeptide with a reasonable expectation of success given that Cajot et al. specifically teaches that both p53 positive and p53 negative tumors can be inhibited by expression of exogenous p53." Examiner's Answer, page 13.

Appellant argues that the prior art does not support a prima facie conclusion of obviousness. Appellant argues that, if the claimed method was considered in the context of the prior art as a whole, a person of ordinary skill in the art would not have had a reasonable expectation that the claimed method would be successful. See the Appeal Brief, pages 17 and 18-19. Appellant also argues that the experiments disclosed by Cajot suffer from serious scientific flaws, "reducing its probative value to a nullity." Appeal Brief, pages 13 and 19-21. Appellant also argues that Katayose and Srivastava "evidence confusion in the field," and in any case are not prior art because they were removed by Appellant's 131 declaration. Appeal Brief, pages 13-18. Finally, Appellant argues that he has presented evidence of unexpected results, which overcome any prima facie case that might be established by the cited references. Appeal Brief, pages 21-23.

"The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be

carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and expectation of success must be founded in the prior art, not in the applicant's disclosure." In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) (citations omitted).

Obviousness under 35 U.S.C. § 103 is established if a preponderance of the evidence in the record supports the obviousness of the claimed invention. See In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443,1445 (Fed. Cir. 1992) ("[T]he conclusion of obviousness vel non is based on the preponderance of evidence and argument in the record."). In this case, both Appellant and the examiner have substantial evidentiary support for their positions; it would be a close question which has the weight of the evidence on their side. We need not weigh the evidence on each side so closely, however, because we conclude that the examiner has not relied on the most relevant prior art references in the record.

2. Rule 131

In the Final Rejection, the examiner relied on Katayose and Srivastava, in the alternative, in addition to the references relied on in the Examiner's Answer. As discussed above, Appellant filed a 131 declaration that pointed to two scientific papers that were published before Katayose or Srivastava, averred that the examiner treated these earlier papers as anticipatory references, and stated that Appellant was in possession of more data than Katayose or Srivastava, prior to the publication of

Katayose or Srivastava. See pages 4-5, supra. The examiner withdrew her reliance on Katayose and Srivastava in response to the 131 declaration.

When faced with a rejection based on a reference that is prior art under 35 U.S.C. §§ 102(a) or 102(e), a patent applicant may attempt to remove the reference as prior art by filing a declaration under 37 CFR § 1.131. "The purpose of filing a 131 declaration is to demonstrate that the applicant's date of invention is prior to the effective date of the reference cited in support of a rejection." In re Asahi/America Inc., 68 F.3d 442, 445, 37 USPQ2d 1204, 1206 (Fed. Cir. 1995). Thus, an effective Rule 131 declaration must show either "reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice." 37 CFR § 1.131(b). It is the applicant's burden to decipher Rule 131 declaration evidence and explain its content. See In re Borkowski, 505 F.2d 713, 718, 184 USPQ 29, 33 (CCPA 1974).

In this case, the declaration does not allege either "reduction to practice prior to the effective date of the reference[s], or conception of the invention prior to the effective date of the reference[s] coupled with due diligence," as required by Rule 131. The declaration therefore fails to satisfy the express terms of the rule.

Instead, the declaration purports to antedate Katayose and Srivastava by "demonstrat[ing] that [Appellant] had achieved the subject matter they disclose in the United States at least as of their date of publication." Paragraph 4. Appellant contends

that because he had in his "possession at least equivalent, and indeed more extensive, data than is taught in the Katayose and Srivastava references at a time prior to their respective publication dates," id., paragraph 5, he has removed the references as prior art.

Appellant's position is not entirely without support in the case law. See, e.g., In re Stempel, 241 F.2d 755, 759, 113 USPQ 77, 81 (CCPA 1957) ("[U]nder the law all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show.") However, the Stempel standard has long since been limited to the situation where the reference being antedated showed a species within a later-claimed genus. See In re Tanczyn, 347 F.2d 830, 832, 146 USPQ 298, 300 (CCPA 1965). The Tanczyn court distinguished that situation from one in which the claims were rejected under § 103 over a combination of references. See id. at 832, 146 USPQ at 300-301 ("The mere fact that an applicant has previously produced that which is disclosed by a reference, however, may have no bearing on the problem of whether he made his invention or a patentable portion of it before the date of a reference."). The Tanczyn court concluded that

> [t]he primary consideration is whether, in addition to showing what the reference shows, the affidavit also establishes possession of either the whole invention claimed or something falling within the claim, in the sense that the claim as a whole reads on it.

> It is not sufficient to show in a Rule 131 affidavit that an invention wholly outside of that being claimed was made prior to the reference date. Such fact is irrelevant.

Id. at 833,146 USPQ at 301 (emphasis in original). See also Borkowski, 505 F.2d at 719, 184 USPQ at 33-34 (Rule 131 requires "a factual showing of completion of the invention before the critical date.").

Here, Appellant's 131 declaration does not assert that the research papers he relies on show "possession of either the whole invention claimed or something falling within the claim, in the sense that the claim as a whole reads on it," as required to antedate the Katayose and Srivastava references. See Tanczyn, 347 F.2d at 833, 146 USPQ at 301. Appellant asserts only that he had in his "possession at least equivalent, and indeed more extensive, data than is taught in the Katayose and Srivastava references at a time prior to their respective publication dates." 131 declaration, paragraph 5. The Tanczyn court, however, noted that "[t]he mere fact that an applicant has previously produced that which is disclosed by a reference . . . may have no bearing on the problem of whether he made his invention or a patentable portion of it before the date of a reference." Tanczyn, 347 F.2d at 832, 146 USPQ at 300-301.

It is Appellant's burden to decipher the declaration evidence and explain its content. See Borkowski, 505 F.2d at 718, 184 USPQ at 33. Appellant's 131 declaration makes no attempt to explain the evidence relied on, i.e., the data in the Liu

and Clayman papers, and the data in the published papers do not appear to show reduction to practice of the method now claimed.

The instant claims are directed to treatment of "a mammalian subject with a solid tumor." See claim 1. Both papers, by contrast, disclose experiments in which the growth of tumor cells injected into nude mice was prevented by adenoviral vectors expressing p53. See Clayman, page 1, abstract ("[W]e prevented the establishment of tumors in nude mice in which tumor cells had been s.c. implanted by transiently introducing exogenous wild-type p53 via an adenoviral vector 2 days following tumor cell implantation."); Liu, page 3117, abstract ("For in vivo analysis of apoptosis, nude mice in which squamous cell carcinoma of the head and neck cell lines had been implanted s.c. had exogenous wt-p53 transiently introduced to the tumor cells via Ad5CMV-p53 2 days later. In situ end labeling clearly illustrated apoptosis in the tumor cells."). Since the methods disclosed in the papers are directed to prevention of tumor cell growth, the papers do not show treatment of "a mammalian subject with a solid tumor."

Appellant's 131 declaration does not aver that the papers show reduction to practice of the instant claims. Nor does the declaration aver that the papers show conception of the method now claimed, plus diligence. All that the declaration avers is that Appellant had in his possession the same data disclosed by Katayose and Srivastava, before their respective dates of publication. This showing is facially

inadequate to antedate the references, and the examiner erred in withdrawing Katayose and Srivastava as prior art based on the 131 declaration.

3. Conclusion

The disclosures of Katayose and Srivastava are very relevant to the claimed method. Both Katayose and Srivastava disclose treatment of $p53^+$ tumor cells using adenoviral vectors which express wild-type p53, just as in the claimed method and in contrast to the experiments disclosed by Cajot, Baker, and Casey,[5] all of whom use a plasmid vector. Katayose and Srivastava both show positive results using the adenoviral vector. Thus, Katayose and Srivastava appear to be very relevant to the issue of the patentability of the instant claims under 35 U.S.C. § 103. Since Katayose and Srivastava are apparently available as prior art under 35 U.S.C. § 102(a), the evidence they disclose should be considered in the obviousness analysis.

The obviousness or nonobviousness of a claimed invention should be determined based on the most relevant prior art. See In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991); (The test of obviousness is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention."); In re Hedges, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986)

[5] Baker et al., "Suppression of human colorectal carcinoma cell growth by wild-type p53," Science, Vol. 249, pp. 912-915 (1990), and Casey et al., "Growth suppression of human breast cancer cells by the introduction of a wild-type p53 gene," Oncogene, Vol. 6, pp. 1791-1797 (1991), are cited by Appellant as evidence showing that those skilled in the art would not have had a reasonable expectation of success in practicing the claimed method.

(When determining obviousness, "the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill."). Since we conclude that the rejection on appeal does not rely on the most relevant prior art in the record, we vacate that rejection and remand the application to the examiner.

Upon return of this application, the examiner should reconsider whether Appellant's declaration meets the requirements of 37 CFR § 1.131 with respect to the claimed invention and review the patentability of the claimed process based on the prior art as a whole. After doing so, she should reject the claims, if appropriate, based on the best available prior art.

Summary

Appellant's Rule 131 declaration is facially defective and should not have been found sufficient to antedate Katayose and Srivastava. Since the evidence provided by Katayose and Srivastava may be crucial to the patentability of the claims on appeal, we vacate the rejection and remand.

VACATED AND REMANDED

SHERMAN D. WINTERS)
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DEMETRA J. MILLS) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
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